REMARKS

Status of the claims

Upon entry of these remarks, claims 31, 36, 38 and 64-77 will be pending in this application. Claims 64-75 have been withdrawn. Claims 76 and 77 have been added. Claims 1, 22, 23, 25 to 28, 33, 34, and 33 to 63 have been cancelled herein. Claims 2 to 21, 24, 29, 30, 32, 35 and 37 were cancelled previously. Applicants reserve the right to pursue the subject matter of the cancelled claims in one or more continuing or divisional applications.

Claims 64-75 have been withdrawn by the Examiner as drawn to non-elected subject matter. Applicants added these claims in their response dated March 8, 2004 and intended them to be part of the elected Group. Applicants submit that the subject matter of claim 64-75 are fully supported by the specification as filed and fall within the scope of elected Group VIII as defined by the Examiner. Applicants respectfully request that the Examiner consider these claims for prosecution along with claims 31, 36 and 38 instead of withdrawing them from consideration.

Amendments to the claims

Claim 31, has been amended such that it is directed to the treatment of Sjögren's Syndrome. Claim 31 has also been amended to require that the recited antibody "inhibits B cell proliferation or immunoglobulin production." Support for this amendment may be found throughout the specification as filed, for example, in paragraphs [0350], [0108], and [0178].

Claims 36 and 38 have been amended to replace the word "administering" with the phrase "contacting a B cell with" and to delete the phrase "to a patient in need thereof." Dependent claims 76 and 77 have been added directed to the methods of claims 36 or 38, respectively, "which is *in vitro*." Support for these amendments may be found throughout the specification as filed, for example, in Example 13 and paragraphs [0180] and [0796].

No new matter has been added by way of amendment, and Applicants respectfully request entry of this amendment.

The Claimed Subject Matter Has Utility Under 35 U.S.C. § 101

Claims 31, 36 and 38[1] were rejected under 35 U.S.C. § 101 for allegedly not being supported by either a specific and substantial asserted utility or a well established utility. The basis for the Examiner's rejection is summarized by her statement on page 6, lines 3-5 of the Office Action mailed May 14, 2004:

> [S]ince there is no biological activity disclosed for the TR17 protein, the claimed invention is not supported by either a specific and substantially asserted utility or a well established utility.

Applicants respectfully disagree. The specification does in fact disclose the biological activity of TR17. For example, in paragraph [0350], it is disclosed that TR17 polypeptides of the invention inhibit B cell proliferation and immunoglobulin production. Moreover, the specification states that agonists of TR17 may be used to prevent certain autoimmune diseases. (see, e.g., paragraph [0108]). The specification clearly states that agonists of TR17 may be antibodies (see, e.g., paragraph [0178]. Moreover, Sjögren's Syndrome is listed as an autoimmune disease that may be treated by such compositions of the invention in, for example, paragraph [0467]. Applicants submit that the use of anti-TR17 antibodies for inhibiting B cell proliferation, immunoglobulin production or treating Sjögren's Syndrome are specific and substantial utilities.

The test for a specific utility is whether an asserted utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention, such as use of a complex machine for landfill. *See*, M.P.E.P., 8th edition, revision 2, § 2107.01 at page 2100-32. The disclosed utilities for anti-TR17 antibodies discussed above are specific, in that not every antibody may be used to inhibit B cell proliferation, inhibit immunoglobulin production or treat Sjögren's Syndrome. Furthermore, where an applicant discloses a biological activity (*e.g.*, the inhibition of B cell proliferation or immunoglobulin production), and reasonably correlates that activity to a disease or condition (*e.g.*, treating an autoimmune disease such as Sjögren's Syndrome), the applicant has sufficiently identified a specific utility for the invention.

[1] In the Office Action, the Examiner indicated claim 37, not 38 was rejected, but Applicants assume claim 38 was meant because claim 37 is cancelled and claim 38 is currently the only other claim belonging to elected Group VIII.

Ibid. Stated in other words, so long as the correlation between the biological activity and the asserted use in a particular disease or condition, is sufficient to convince one of skill in the art, then the specificity requirement of 35 U.S.C. § 101 is satisfied. *See also, Fujikawa v. Wattanasin*, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996). Applicants submit that it was known as of the earliest filing date of the present application that Sjögren's Sydrome was a B cell mediated autoimmune disease characterized by aberrant B cell proliferation and immunoglobulin secretion. Accordingly, Applicants asserted utility is specific.

Moreover, the disclosed utilities for anti-TR17 antibodies discussed above are substantial, as "the general rule [is] that the treatments of specific diseases or conditions meet the criteria of 35 U.S.C. § 101." *See*, M.P.E.P., 8th edition, revision 2, § 2107.01 at pages 2100-32 to 2100-33. Pharmacological or therapeutic inventions that provide any "immediate benefit to the public" satisfy 35 U.S.C. § 101. *See, Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980); *See also,* M.P.E.P. §2107.01(III). It is well-established that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and satisfies the utility requirement. *Id* at page 2100-34. Accordingly, the utilities asserted by Applicants are clearly substantial.

The last requirement for a specific and substantial utility is that it must be credible to one of skill in the art (M.P.E.P., 8th edition, revision 2, § 2107 (II)(B) at pages 2100-29). Applicants also respectfully remind the examiner that post-filing date data maybe used to confirm an asserted utility. The Federal Circuit held in *In re Brana*, evidence dated after the filing date "can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." 51 F. 3d. 1560, 1567 at n19 (Fed. Cir. 1995). Such evidence "goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)." *Id., citing In re Marzocchi*, 439 F2d. at 224 n.4, 169 U.S.P.Q. at 370 n.4.

Applicants submit herewith an article by Seshasyaee et al. (Seshasyaee et al, "Loss of TACI causes fatal lymphoproliferation and autoimmunity, establishing TACI as an inhibitory BLyS Receptor, " *Immunity* (2003) 18:279-288, cited in the Information Disclosure Statement submitted herewith as reference B1) which demonstrates the accuracy of Applicants asserted utilities. TACI was identified as a receptor for the cytokine BLyS in the Gross et al. 2000 reference cited in the Introduction of Seshasyaee et

al. Applicants submit herewith a copy of the GenBank report for the TACI protein identified by Gross et al. (GenBank Accession Number NP_036584, Exhibit A) and an alignment of the protein of SEQ ID NO:2 with TACI (Exhibit B) demonstrating that TR17 of the invention is TACI. In the introduction, Seshasyaee et al. describe results by others (Yan et al., cited in the Information Disclosure Statement submitted herewith as reference B2) that indicate that ablation of TACI function in transgenic mice results in B cell hyerplasia and increased production of immunoglobulins in vitro. Seshasyaee et al. confirm the results of Yan et al., showing that TACI knockout mice have a lymphproliferative phenotype (Figure 1) accompanied by autoimmune like symptoms including increased levels of autoantibodies (Figures 3B and 3C). Seshasyaee et al. extends their results by showing that agonistic anti-TACI antibodies inhibit B cell proliferation in vitro (see, p. 283, section entitled "Activation of the TACI Intracellular Domain Inhibits B Cell Proliferation In Vitro"). Taken together, these results substantiate the accuracy of the utility asserted in the specification: inhibiting B cell proliferation, inhibiting immunoglobulin production or treating Sjögren's Syndrome.

In addition, Applicants reiterate that

> "[k]nowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illness and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose as many pharmacological activities as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility."

Nelson v. Bowler, 626 F.2d 853, 856 (C.C.P.A. 1980) and See, *Cross v. Iizuka* 753 F 2d 1040, 1050 (1985) citing same. The ability of anti-TR17 antibodies to inhibit B cell proliferation or immunoglobulin production is such a pharmacologcial activity which under case law constitutes a showing of practical utility." *Id.* Furthermore, utility can exist for therapeutic inventions "despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition." M.P.E.P, 8th edition, 2107 (III) at 2100-35.

In summary, it is clear that the specification describes a biological role for the TR17 protein that provides a basis for a specific, substantial, as well as credible (indeed confirmed), utility for the claimed methods, that is firmly corroborated by the literature.

Thus Applicants have met the burden of showing that the claimed invention has a specific and substantial utility that is credible, and therefore, Applicants respectfully request that the Examiner withdraw the rejection under § 101.

The Claimed Subject Matter is Enabled Under 35 U.S.C. § 112, first paragraph

Claims 31, 36 and 38[2] were rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement More specifically, the Examiner maintains that use of an anti-TR17 antibody as a therapeutic agent is highly unpredictable based on the state of the art. The Examiner relies on three articles: Fox et al., Molina et al., and Canhao et al. (See Office Action Mailed May 14, 2004 page 7, lines 17-19 and page 9, lines 1-10). The Examiner states that there is no guidance in the specification or working examples. (See Office Action Mailed May 14, 2004 page 7, lines 16-17 and page 8, lines 9-12). Lastly, the Examiner indicates that practicing the invention as claimed would require the "*de novo* determination [of] pharmaceutical formulations of antibody" with "known antibodies against known proteins with signs and symptoms to correlate with inhibition[3] of the target protein" which the Examiner considers to be undue experimentation (See Office Action Mailed May 14, 2004 page 8, lines 1-6).

Applicants respectfully disagree.

Use of antibodies as therapeutic agents is not the highly unpredictable art that the Examiner maintains it is. Preliminarily, Applicants note that both the Fox and the Molina references can hardly be considered the "state of the art" as of the earliest priority date of the instant application (March 10, 2000) because they were published in 1997 and 1996, respectively. Three or four years in the field of biotechnology is ample time for significant advances to be made in the field of biotechnology. Moreover, the Molina and the Canhao references describe the use of ***non-specific*** polyclonal populations of intravenous immunoglobulin (IVIG) in the treatment of neurological conditions associated with Sjögren's Syndrome. These references do not report on the use of protein-specific antibody compositions and therefore are not particularly relevant to the state of the art in the field of the claimed invention which requires the use of TR17 **specific** antibodies.

[2] In the Office Action, the Examiner indicated claim 37, not 38 was rejected, but Applicants assume claim 38 was meant because claim 37 is cancelled and claim 38 is currently the only other claim belonging to elected Group VIII.

Lastly, the Examiner takes the statement in the Fox reference that specific antibody compositions such as anti-TNF antibody, which has been used successfully in the treatment of rheumatoid arthritis, could potentially have therapeutic use in the treatment of Sjögren's Syndrome after controlled trials have been performed as evidence that the use of antibody therapies is highly unpredictable. Applicants disagree. Instead, Applicants submit that this statement indicates that in rheumatoid arthritis (a B cell–mediated autoimmune disease like Sjögren's Syndrome), a specific antibody composition has been used successfully. Moreover, the need for controlled trials simply reflects the need to establish routine dosing regimens and monitor for safety and efficacy considerations as required by the Food and Drug Administration, none of which falls in the category of undue experimentation. Applicants remind the Examiner that, as stated in M.P.E.P., 8th edition, revision 2, § 2164.05 at page 2100-190, "considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. See *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ('Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA].')."

Furthermore, Applicants direct the Examiner's attention to section 2164.01(c) of the M.P.E.P., (8th edition, revision 2) which states that:

> If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied. *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
>
> For example, it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph. The applicant need not demonstrate that the invention is completely safe. See also M.P.E.P. § 2107.01 and § 2107.03.

---

[3] Applicants note for the record that inhibition of TR17 is not required by the claims, only that the antibody specifically bind TR17.

Applicants submit that as of the earliest effective priority date of the present application there have been art recognized standards for determining pharmaceutical formulations for antibodies. Illustrative of this point, Box 5 from Waldmann, TA, "Immunotherapy: Past, Present and Future" *Nature Medicine* (2003) 9:269-277, (cited in the Information Disclosure Statement submitted herewith as reference B3), shows that several monoclonal antibodies were already approved by the United States Food and Drug Administration for administration to humans or in late stage human clinical trials at the time of the earliest effective priority date of the present application. This demonstrates that there were art recognized methods for determining the pharmaceutical formulations of antibodies for administration to human (clinical trials) and animal subjects (pre-clinical experimentation). Therefore, Applicants submit the application meets the enablement standards under 35 U.S.C. § 112, first paragraph.

Moreover, the Examiner seems to suggest that this claimed invention cannot be enabled unless an actual antibody had been made and characterized (See reference to "known antibodies" on page 8, line 3 of the Office Action mailed May 14, 2004).

Applicants disagree. According to the Federal Circuit, "a considerable amount of experimentation is permissible, if it is merely routine" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Jackson*, 217 USPQ 804 (Board of Patent Appeals and Interferences, 1982)). Additionally, Applicants remind the Examiner that while the predictability of the *art* can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the *result* of the experiment is not a consideration. Indeed, the Court of Custom and Patent Appeals has specifically cautioned that the unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue in *In re Angstadt*, 190 USPQ 214 (C.C.P.A. 1976):

> [If to fulfill the requirements of 112, first paragraph, an applicant's] disclosure must provide guidance which will enable one skilled in the art to determine, with reasonable certainty before performing the reaction whether the claimed product will be obtained, . . . then all "experimentation" is "undue" since the term "experimentation" implies that the success of the particular activity is uncertain. Such a proposition is contrary to the basic policy of the Patent Act.

Id. at 219 (emphasis in the original). As Judge Rich explained in *In re Vaeck*, 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991), the statutory enablement

requirement is satisfied if the specification "adequately guides the worker to *determine*, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility" (emphasis provided).

Methods of making specific antibodies has been acknowledged by the Federal Circuit to be routine technology. *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988); *Hybritech Incorporated v. Monoclonal Antibodies Inc.,* 231 USPQ 81 (Fed. Cir. 1986). Similarly, methods of determining B cell proliferation assays and assays for determining immunoglobulin production were also known in the art as of the earliest effective priority date of the present application. In support of this assertion, Applicants direct the Examiner's attention to Examples 13 and 14 of the specification as filed which describe a standard B cell proliferation assay that could be used to assess anti-TR17 antibodies. Applicants also submit herewith a copy of Moore et al., (Moore et al., "BLyS: Member of the Tumor Necrosis Factor Family and B Lymphocyte Stimulator," Science (1999) 285:260-263, cited in the Information Disclosure Statement submitted herewith as reference B4) which demonstrates use of a similar B cell proliferation assay. In the paragraph describing the B cell proliferation assay (see paragraph spanning pages 260-261), Moore et al. indicate this assay has been known in the art for some time by citing references that date back to 1977 and 1978 (references 7, 8). Moreover, Applicants submit that one of skill in the art could easily adapt the assay to assess the effect of anti-TR17 antibodies on B cells stimulated with either anti-IgM or Staphylococcus Aureus Cowan (SAC) alone or with either of these agents in combination with BLyS (also known as Neutrokine-alpha, which is identified in the specification as a ligand for TR17 in, for example, paragraph [0037]). Similarly, assays such as ELISA assays for measuring immunoglobulin production have also been known in the art for some time (see, for example, Figure 4C of Moore et al.) Applicants also refer the Examiner to Rousset et al., (Cytokine-induced Proliferation and Immunoglobulin Production of Human B lymphocytes Triggered through their CD40 Antigen, The Journal of Experimental Medicine (1991) 173:705-710, which is cited in the Information Disclosure Statement submitted herewith as reference B5) which shows that ELISA assays for detecting immunoglobulin production were a standard technology even in 1991 (see paragraph spanning pages 705-706, paragraph spanning pages 707-708 and Table 1). Moreover, it was known as of the earliest filing date of the present application that Sjögren's Sydrome

was a B cell mediated autoimmune disease characterized by aberrant B cell proliferation and immunoglobulin secretion. Accordingly, one of skill in the art would not have had to engage in undue experimentation to make and characterize anti-TR17 antibodies for their ability to inhibit B cell proliferation or to induce immunoglobulin production, and therefore to be useful in the treatment of Sjögren's Syndrome. Accordingly, Applicants submit the enablement requirement of 35 U.S.C. § 112, first paragraph has been met and respectfully request that the Examiner reconsider and withdraw this objection.

The Claimed Subject Matter is Adequately Described Under 35 U.S.C. § 112, first paragraph

Claims 31, 36 and 38[4] were rejected under 35 U.S.C. § 112, first paragraph for allegedly containing subject matter which was not descried in the specification in such a manner as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed had possession of the claimed invention. Mores specifically, the Examiner states,

> The claims require "an antibody or fragment thereof that is immunoreactive to TR17 protein"[5] while practicing the claimed methods. The claims, however, do not require that the antibody to possess any particular conserved structure, or other distinguishing feature, such as a specific biological activity. Thus, binding to TR17 protein draws the claims to a genus of antibodies that is defined by the desired activity to inhibit TR17 protein activity." See Office Action Mailed May 14, 2004 page 9, lines 15-19.

Applicants respectfully disagree. Preliminarily, Applicants note that the claims do not require that "TR17 activity" be inhibited, merely that the recited antibodies specifically bind TR17 and in the case of claims 36 and 38 result in the inhibition of B cell proliferation or immunoglobulin production, respectively.

Moreover, Applicants direct the Examiner's attention to Example 16 of *Revised Interim Written Description Guidelines Training Material* available from the USPTO website at http://www.uspto.gov/web/patents/guides.htm. The analysis section of this example makes it clear that the United States Patent and Trademark Office considers that

[4] In the Office Action, the Examiner indicated claim 37, not 38 was rejected, but Applicants assume claim 38 was meant because claim 37 is cancelled and claim 38 is currently the only other claim belonging to elected Group VIII.

the antibody art is "well developed and mature;" that it is routine to make antibodies to fully characterized antigens (e.g. TR17 of SEQ ID NO:2); and that antibodies have "well defined structural characteristics." (see page 60 of *Revised Interim Written Description Guidelines Training Material*). Accordingly, The Examiner's position that the claims should state or refer to a particular conserved structure for the recited antibodies in contrary to established Patent Office practice. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

The Examiner is invited to call the undersigned at the phone number provided below if any further action by Applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Dated: October 14, 2004

Respectfully submitted,

By Michele Shannon

Michele Shannon
Registration No.: 47,075
HUMAN GENOME SCIENCES, INC.
Intellectual Property Dept.
14200 Shady Grove Road
Rockville, Maryland 20850
(301) 354-3930

KKH/MS/ba

[5] Applicants note this is not a direct quote of the claim language which recited "an antibody of fragment thereof that **specifically binds** a TR17 protein...".

Blast 2 Sequences results

PubMed Entrez BLAST OMIM Taxonomy Structure

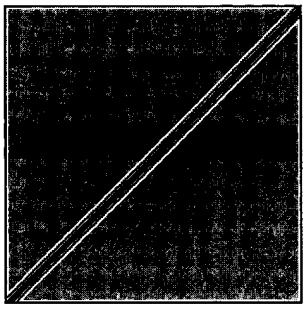
BLAST 2 SEQUENCES RESULTS VERSION BLASTP 2.2.9 [May-01-2004]

Matrix BLOSUM62 gap open: 11 gap extension: 1

x_dropoff: 50 expect: 10.000 wordsize: 3 Filter ☐ Align

Sequence lcl|NP_036584 **Length** 293 (1 .. 293)

Sequence lcl|SEQ ID NO:2 **Length** 293 (1 .. 293)



NOTE:The statistics (bitscore and expect value) is calculated based on the size of nr database

```
Score =  631 bits (1627), Expect = e-179
Identities = 293/293 (100%), Positives = 293/293 (100%)
```

```
Query: 1   MSGLGRSRRGGRSRVDQEERFPQGLWTGVAMRSCPEEQYWDPLLGTCMSCKTICNHQSQR 60
           MSGLGRSRRGGRSRVDQEERFPQGLWTGVAMRSCPEEQYWDPLLGTCMSCKTICNHQSQR
Sbjct: 1   MSGLGRSRRGGRSRVDQEERFPQGLWTGVAMRSCPEEQYWDPLLGTCMSCKTICNHQSQR 60

Query: 61  TCAAFCRSLSCRKEQGKFYDHLLRDCISCASICGQHPKQCAYFCENKLRSPVNLPPELRR 120
           TCAAFCRSLSCRKEQGKFYDHLLRDCISCASICGQHPKQCAYFCENKLRSPVNLPPELRR
Sbjct: 61  TCAAFCRSLSCRKEQGKFYDHLLRDCISCASICGQHPKQCAYFCENKLRSPVNLPPELRR 120

Query: 121 QRSGEVENNSDNSGRYQGLEHRGSEASPALPGLKLSADQVALVYSTLGLCLCAVLCCFLV 180
           QRSGEVENNSDNSGRYQGLEHRGSEASPALPGLKLSADQVALVYSTLGLCLCAVLCCFLV
Sbjct: 121 QRSGEVENNSDNSGRYQGLEHRGSEASPALPGLKLSADQVALVYSTLGLCLCAVLCCFLV 180

Query: 181 AVACFLKKRGDPCSCQPRSRPRQSPAKSSQDHAMEAGSPVSTSPEPVETCSFCFPECRAP 240
           AVACFLKKRGDPCSCQPRSRPRQSPAKSSQDHAMEAGSPVSTSPEPVETCSFCFPECRAP
Sbjct: 181 AVACFLKKRGDPCSCQPRSRPRQSPAKSSQDHAMEAGSPVSTSPEPVETCSFCFPECRAP 240

Query: 241 TQESAVTPGTPDPTCAGRWGCHTRTTVLQPCPHIPDSGLGIVCVPAQEGGPGA 293
           TQESAVTPGTPDPTCAGRWGCHTRTTVLQPCPHIPDSGLGIVCVPAQEGGPGA
Sbjct: 241 TQESAVTPGTPDPTCAGRWGCHTRTTVLQPCPHIPDSGLGIVCVPAQEGGPGA 293

CPU time:     0.02 user secs.          0.01 sys. secs          0.03 total secs.

Lambda      K       H
   0.320    0.135    0.450

Gapped
Lambda      K       H
   0.267   0.0410    0.140


Matrix: BLOSUM62
Gap Penalties: Existence: 11, Extension: 1
Number of Sequences: 1
```

Number of Hits to DB: 1241
Number of extensions: 596
Number of successful extensions: 3
Number of sequences better than 10.0: 1
Number of HSP's better than 10.0 without gapping: 1
Number of HSP's gapped: 1
Number of HSP's successfully gapped: 1
Number of extra gapped extensions for HSPs above 10.0: 0
Length of query: 293
Length of database: 702,241,455
Length adjustment: 128
Effective length of query: 165
Effective length of database: 702,241,327
Effective search space: 115869818955
Effective search space used: 115869818955
Neighboring words threshold: 9
Window for multiple hits: 0
X1: 16 (7.4 bits)
X2: 129 (50.0 bits)
X3: 129 (50.0 bits)
S1: 41 (22.0 bits)
S2: 75 (33.5 bits)

☐ 1: NP_036584. tumor necrosis fa...[gi:6912694] BLink, Links

```
LOCUS       NP_036584                293 aa            linear   PRI 23-AUG-2004
DEFINITION  tumor necrosis factor receptor 13B; transmembrane activator and
            CAML interactor [Homo sapiens].
ACCESSION   NP_036584
VERSION     NP_036584.1  GI:6912694
DBSOURCE    REFSEQ: accession NM_012452.2
KEYWORDS    .
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Primates; Catarrhini; Hominidae; Homo.
REFERENCE   1  (residues 1 to 293)
  AUTHORS   Novak,A.J., Darce,J.R., Arendt,B.K., Harder,B., Henderson,K.,
            Kindsvogel,W., Gross,J.A., Greipp,P.R. and Jelinek,D.F.
  TITLE     Expression of BCMA, TACI, and BAFF-R in multiple myeloma: a
            mechanism for growth and survival
  JOURNAL   Blood 103 (2), 689-694 (2004)
   PUBMED   14512299
  REMARK    GeneRIF: Expression of BCMA, TACI, and BAFF-R by multiple myeloma
            cells support cell growth and survival.
REFERENCE   2  (residues 1 to 293)
  AUTHORS   Wu,Y., Bressette,D., Carrell,J.A., Kaufman,T., Feng,P., Taylor,K.,
            Gan,Y., Cho,Y.H., Garcia,A.D., Gollatz,E., Dimke,D., LaFleur,D.,
            Migone,T.S., Nardelli,B., Wei,P., Ruben,S.M., Ullrich,S.J.,
            Olsen,H.S., Kanakaraj,P., Moore,P.A. and Baker,K.P.
  TITLE     Tumor necrosis factor (TNF) receptor superfamily member TACI is a
            high affinity receptor for TNF family members APRIL and BLyS
  JOURNAL   J. Biol. Chem. 275 (45), 35478-35485 (2000)
   PUBMED   10956646
REFERENCE   3  (residues 1 to 293)
  AUTHORS   Yu,G., Boone,T., Delaney,J., Hawkins,N., Kelley,M.,
            Ramakrishnan,M., McCabe,S., Qiu,W.R., Kornuc,M., Xia,X.Z., Guo,J.,
            Stolina,M., Boyle,W.J., Sarosi,I., Hsu,H., Senaldi,G. and
            Theill,L.E.
  TITLE     APRIL and TALL-I and receptors BCMA and TACI: system for regulating
            humoral immunity
  JOURNAL   Nat. Immunol. 1 (3), 252-256 (2000)
   PUBMED   10973284
REFERENCE   4  (residues 1 to 293)
  AUTHORS   von Bulow,G.U., Russell,H., Copeland,N.G., Gilbert,D.J.,
            Jenkins,N.A. and Bram,R.J.
  TITLE     Molecular cloning and functional characterization of murine
            transmembrane activator and CAML interactor (TACI) with chromosomal
            localization in human and mouse
  JOURNAL   Mamm. Genome 11 (8), 628-632 (2000)
   PUBMED   10920230
REFERENCE   5  (residues 1 to 293)
  AUTHORS   Xia,X.Z., Treanor,J., Senaldi,G., Khare,S.D., Boone,T., Kelley,M.,
            Theill,L.E., Colombero,A., Solovyev,I., Lee,F., McCabe,S.,
            Elliott,R., Miner,K., Hawkins,N., Guo,J., Stolina,M., Yu,G.,
            Wang,J., Delaney,J., Meng,S.Y., Boyle,W.J. and Hsu,H.
  TITLE     TACI is a TRAF-interacting receptor for TALL-1, a tumor necrosis
            factor family member involved in B cell regulation
  JOURNAL   J. Exp. Med. 192 (1), 137-143 (2000)
   PUBMED   10880535
REFERENCE   6  (residues 1 to 293)
  AUTHORS   Yan,M., Marsters,S.A., Grewal,I.S., Wang,H., Ashkenazi,A. and
```

Dixit,V.M.
TITLE Identification of a receptor for BLyS demonstrates a crucial role in humoral immunity
JOURNAL Nat. Immunol. 1 (1), 37-41 (2000)
PUBMED 10881172
REFERENCE 7 (residues 1 to 293)
AUTHORS Marsters,S.A., Yan,M., Pitti,R.M., Haas,P.E., Dixit,V.M. and Ashkenazi,A.
TITLE Interaction of the TNF homologues BLyS and APRIL with the TNF receptor homologues BCMA and TACI
JOURNAL Curr. Biol. 10 (13), 785-788 (2000)
PUBMED 10898980
REFERENCE 8 (residues 1 to 293)
AUTHORS Gross,J.A., Johnston,J., Mudri,S., Enselman,R., Dillon,S.R., Madden,K., Xu,W., Parrish-Novak,J., Foster,D., Lofton-Day,C., Moore,M., Littau,A., Grossman,A., Haugen,H., Foley,K., Blumberg,H., Harrison,K., Kindsvogel,W. and Clegg,C.H.
TITLE TACI and BCMA are receptors for a TNF homologue implicated in B-cell autoimmune disease
JOURNAL Nature 404 (6781), 995-999 (2000)
PUBMED 10801128
REFERENCE 9 (residues 1 to 293)
AUTHORS von Bulow,G.U. and Bram,R.J.
TITLE NF-AT activation induced by a CAML-interacting member of the tumor necrosis factor receptor superfamily
JOURNAL Science 278 (5335), 138-141 (1997)
PUBMED 9311921
COMMENT REVIEWED REFSEQ: This record has been curated by NCBI staff. The reference sequence was derived from AF023614.1.

Summary: The protein encoded by this gene is a lymphocyte-specific member of the tumor necrosis factor (TNF) receptor superfamily. It interacts with calcium-modulator and cyclophilin ligand (CAML). The protein induces activation of the transcription factors NFAT, AP1, and NF-kappa-B and plays a crucial role in humoral immunity by interacting with a TNF ligand. This gene is located within the Smith-Magenis syndrome region on chromosome 17.

FEATURES Location/Qualifiers

source 1..293
/organism="Homo sapiens"
/db_xref="taxon:9606"
/chromosome="17"
/map="17p11.2"

Protein 1..293
/product="tumor necrosis factor receptor 13B"
/note="transmembrane activator and CAML interactor"

Region 34..66
/region_name="cysteine-rich TNFR repeat"

Region 71..104
/region_name="cysteine-rich TNFR repeat"

Region 167..186
/region_name="transmembrane domain"

CDS 1..293
/gene="TNFRSF13B"
/coded_by="NM_012452.2:14..895"
/note="go_component: integral to plasma membrane [goid 0005887] [evidence TAS] [pmid 9311921];
go_function: receptor activity [goid 0004872] [evidence TAS] [pmid 9311921];
go_process: immune response [goid 0006955] [evidence IEA];
go_process: cell surface receptor linked signal transduction [goid 0007166] [evidence TAS] [pmid 9311921]"
/db_xref="GeneID:23495"
/db_xref="LocusID:23495"
/db_xref="MIM:604907"

ORIGIN

```
        1 msglgrsrrg grsrvdqeer fpqglwtgva mrscpeeqyw dpllgtcmsc kticnhqsqr
       61 tcaafcrsls crkeqgkfyd hllrdcisca sicgqhpkqc ayfcenklrs pvnlppelrr
      121 qrsgevenns dnsgryqgle hrgseaspal pglklsadqv alvystlglc lcavlccflv
      181 avacflkkrg dpcscqprsr prqspakssq dhameagspv stspepvetc sfcfpecrap
```

241 tqesavtpgt pdptcagrwg chtrttvlqp cphipdsglg ivcvpaqegg pga
//

Oct 4 2004 14:35:49